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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,661	02/05/2004	Yin-Xiong Li	275.00030103	5608

26813 7590 01/05/2006

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VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/772,661	LI ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-131* is/are pending in the application.

4a) Of the above claim(s) *14,15,28,30-43,52,54-72 and 84-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16-27,29,44-51,53,73-83 and 87-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see box 6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS: 5/04, 10/04, 3/05 & 8/05*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claims 1-13, 16-27, 29, 44-51, 53, 73-83 and 87-131 in the reply filed on October 6, 2005 is acknowledged. The traversal is on the ground(s) that the inventions can be readily evaluated in one search without undue burden on the examiner. This is not found persuasive because applicant has not provided evidence or specific arguments showing the examiner's reasons for restriction set forth in the requirement mailed September 6, 2005, that searches of methods of inhibiting gene expression, double stranded RNAs and methods of conducting a pharmaceutical business are not co-extensive, is in error.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14, 15, 28, 30-43, 52, 54-72 and 84-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 6, 2005.

Priority

This application claims benefit of priority as a continuation of application 10/038,984. However, the instant application contains disclosure not presented in the prior application, specifically the term siRNA in claims 77, 78, 122, 123 and 126 and is

thus a continuation-in-part. Because of the newly added material this application has priority to the instant filing date, February 5, 2004.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

This application is a continuation-in-part, such applications require a newly executed oath as described in 37 CFR 1.63(e).

Claim Objections

Claims 29 and 53 are objected to because of the following informalities: each of these claims recites a limitation that is directed to a non-elected invention and thus contain non-elected subject matter. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16, 17, 21, 22, 27, 29, 44-46, 51, 53, 87-90, 92, 98-101, 108 and 109 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, 18, 39 and 48 of copending Application No. 10/038,984. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '984 application are a species of the instant claims. The claims of the '984 application are directed to methods of attenuating gene expression in an embryonic zebrafish cell *in vitro* or *in vivo* using double stranded

RNA complementary to the target gene. The target gene is endogenous or from a pathogen. The RNA is formed from one or two complementary strands. The instant claims are broad generic claims directed to attenuation of gene expression in cells not limited to zebrafish and thus the species claims of the '984 application would anticipate the instant generic claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 23, 46, 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claims 22, 23, 46 and 47, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 73-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are directed to a method using the compound of a withdrawn claim. Because the subject matter of the withdrawn claims has not been considered, the metes and bounds of the method cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 18-27, 29, 51, 53, 76-83, 87-92, 96-109, 113-126 and 128-131 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of attenuating the expression of target genes in zebrafish cells in culture or zebrafish embryos, in avian neural crest tissue explant culture and in rat cell culture, does not reasonably provide enablement for attenuating gene expression *in vivo* in any non-embryonic animal. Moreover, the specification does not reasonably provide enablement for a method for treating a disease or infection in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claimed invention is directed to methods of inhibiting expression of target genes in cells that may be in an organism using double stranded RNA. The RNA hybridizes with or is identical to all or a portion of the target gene; the target gene is endogenous, cellular, foreign, viral or from a pathogen. The RNA may be formed from a single strand or separate complementary strands and may be produced inside or outside the cell synthetically or by transcription from an expression construct. The claimed invention also includes methods of treating a disease or infection as the target genes may be from pathogens and viruses and some claims are directed to inhibiting gene expression in a "patient", indicating a therapeutic method.

The specification teaches as exemplified embodiments the introduction of specific double stranded RNAs (dsRNAs) with lengths of 141-488 base pairs in zebrafish embryos, avian tissue culture explants, and rat cells. The dsRNAs target a particular gene, causing an attenuation or inhibition of gene expression, resulting in a particular phenotype.

At the time the instant application was filed, and even to date, the unpredictability of attenuating/inhibiting expression of a target gene *in vivo* in animals by RNA interference (RNAi) is evident and nucleic acid based therapies were highly unpredictable. While it is recognized that introduction of dsRNA targeted to a specific gene may result in attenuation of expression of that gene, the degree of attenuation and the length of time of attenuation is not predictable. For example, Fire (Nature 1998, cited on IDS) indicates that introduction of dsRNA can result in a mosaic pattern of interference or resistance to interference may be observed. In addition, Fire teaches that the design of the dsRNA is important because not all dsRNA sequences work well.

With respect to RNAi in vertebrate embryos, the specification provides a working example of targeting well-characterized genes with dsRNA by microinjection in zebrafish embryos. However, two recent reports indicate that RNAi causes non-specific effects in this system. Oates et al. (Developmental Biology 2000, cited on IDS) report that, with regard to the spt gene, which was selected because it is phenotypically and genetically well characterized (see page 21, first column),

> "dsRNA injected into early zebrafish embryos causes a nonspecific depletion of several endogenous mRNAs, leading to an easily misinterpreted syndrome of developmental defects. Thus, at present, RNAi appears unsuited to application in the zebrafish embryo for the study of zygotic gene activity during development."

Similarly, Zhao et al. (Developmental Biology, 2001, cited on IDS) report non-specific defects in zebrafish embryos injected with dsRNA sequences targeting the maternal gene *poulI-1*, the transgene *GFP* and an intron of the zebrafish gene *terra* (see p 215, abstract and pages 220-222). Zhao et al. indicate that the technique needs to be further developed (see page 216, first column, lines 1-3).

At the time of filing, the field of RNA interference was in its infancy and gene specific dsRNA inhibition in mammalian cells was highly unpredictable, particularly because in mammalian cells longer dsRNA molecules were observed to cause induction of the PKR response, an immune response resulting in cell apoptosis and non-specific mRNA expression inhibition that is triggered by even small amounts of double stranded RNA and would preclude the use of dsRNA *in vivo*. After the filing date of this application, the field of RNA interference determined that shorter dsRNA molecules could overcome this PKR response and result in a more predictable inhibitory response, however, guidance for the use of shorter dsRNAs, as discussed in the

literature as necessary to more predictably apply the claimed methods, was not provided in the instant specification.

Wianny et al. (Nature Cell Biology 2000, cited on IDS) have reported that dsRNA can be used as a specific inhibitor of gene activity in the mouse oocyte and preimplantation embryo. However, the authors indicate that it is possible that the early mouse embryo is incapable of an interferon response and that there may still be difficulties in using RNAi at later stages (see page 73, under Discussion). Thus, the post-filing art clearly suggests that administering dsRNA to vertebrate systems *in vivo*, to inhibit target genes is not a reproducible or predictable art.

At the time the instant invention was made and therapeutic use of nucleic acids was a highly unpredictable art; see for example, Opalinska et al. (Nature Reviews Drug Discovery, 2002, cited on IDS), who state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

The claimed invention encompasses methods of treating disease in an organism. With regard to such methods, the specification does not provide sufficient guidance for selecting an appropriate route of administration or amount of the dsRNA required such that a sufficient amount of dsRNA would be taken up by the appropriate tissues and

effectively attenuate gene expression. The specification does not provide any working examples of treating disease or infection in a mammal.

RNA interference methods for therapeutic purposes encounter the same problems long recognized in other nucleic acid based therapies, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

The specification provides a general disclosure of delivery methods and it is noted that while prior art references teach administration of dsRNA to invertebrates using several of these methods (such as microinjection into a body cavity of *C. elegans* and feeding *E. coli* which express dsRNAs to *C. elegans*), the prior art does not address administering dsRNA to vertebrates and thus does not teach successful delivery inhibition of a target gene *in vivo* in vertebrates. Caplen (Expert Opin. Biol. Ther. 2003, cited on IDS) points out (see page 581)

> "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..."

Coburn et al. (Journal of Antimicrobial Chemotherapy. 2003, cited on IDS) also points out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph). Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective,

Check (Nature, 2003, cited on IDS) describes the ongoing difficulties in using RNAi to treat disease and reports at page 11

> "...[S]cientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up."

Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " ...'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page,

> "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all animals, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein long dsRNA is delivered to avian neural crest tissue and rat cells *in vitro*, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of dsRNA to any animal, particularly mammals. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al. (Molecular Medicine Today 2000, cited on IDS) states at page 79-80

> "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides... .*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide."

Agrawal discusses these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro*

versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of dsRNA into animal cells *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful attenuation/inhibition of a target gene. One of skill in the art would not know how to deliver dsRNA to an organism in such a way that would ensure an amount sufficient to attenuate expression of a target gene is delivered to the proper cell.

In fact, the state of the art is such that successful delivery of nucleic acid sequences to a target cell *in vivo* such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of dsRNA for use in RNA interference and for therapeutic use in any animal. The field of RNA interference does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of introducing dsRNA in any animal, as the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Thus, one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-13, 18-27, 29, 51, 53, 76-83, 87-92, 96-109, 113-126 and 128-131 are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7, 9-13, 16-27, 29, 44-51, 53, 87-92, 96-101, 103, 104, 108, 109 and 113-116 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550, cited on IDS).

The claims are directed to methods of inhibiting expression of target genes in cells that may be in an organism using double stranded RNA. The RNA hybridizes with or is identical to all or a portion of the target gene; the target gene is endogenous, cellular, foreign, viral or from a pathogen. The RNA may be formed from a single strand or separate complementary strands.

Agrawal et al. disclose self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On page 15 Agrawal et al. disclose that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region while at page 9, line 30 through page 10 line 1 it is disclosed that the target hybridizing region is complementary to a nucleic acid sequence from a variety of sources including viruses, pathogens, cellular genes or gene

transcripts. Pages 15 and 16 describe embodiments where the oligonucleotide is a single nucleic acid strand that forms a double stranded structure as well as an embodiment where the self-complementary region is connected to the hybridizing region by a non-nucleotide linker, making the self-complementary region and the hybridizing region two separate complementary nucleic acid strands. On pages 17, line 27 through page 18 Agrawal et al. disclose that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animal.

Thus, Agrawal et al. disclose all limitations of and anticipate claims 1-5, 7, 9-13, 16-27, 29, 44-51, 53, 87-92, 96-101, 103, 104, 108, 109 and 113-116.

Claims 1, 2, 6-11, 16-19, 21, 23, 24, 44, 45, 47, 48, 87-92 and 99-102 are rejected under 35 U.S.C. 102(b) as being anticipated by Cameron et al. (Proc. Natl. Acad. Sci. USA 1989, vol. 86, pages 9139-9143).

The claimed invention is directed to a method for inhibiting the expression of a target gene in a mammalian cell, comprising introducing a double stranded structure having a sequence which is substantially identical to a part of the target gene; the target gene may be an endogenous gene and the RNA may be a single self-complementary strand or two separate complementary strands, may be produced within the cell, may be produced recombinantly and may be produced by an expression vector in the cell.

Cameron et al. disclose specific gene suppression by engineered ribozymes in monkey cells. Specifically, Cameron et al. disclose inhibiting endogenous chloramphenicol acetyltranferase (CAT) gene expression in monkey kidney cell line (COS1) cells comprising administering ribozyme nucleic acids (see Figure 2). It is

noted that the ribozyme nucleic acids disclosed by Cameron et al. are double stranded (see Figure 1A) and thus read on the double stranded structure as recited in claims 1 and 87. Cameron et al. further disclose plasmids containing CAT ribozymes were constructed (see Figure 1).

Therefore, Cameron et al. anticipate claims 1, 2, 6-11, 16-19, 21, 23, 24, 44, 45, 47, 48, 87-92 and 99-102.

Claims 120, 127-129 and 131 are rejected under 35 U.S.C. 102(e) as being anticipated by Cowsert (US 5,945,290).

Cowsert discloses antisense oligonucleotides directed to RhoA. At column 2, lines 34-42, Cowsert discloses that RhoA expression can be inhibited by administration of multiple antisense oligonucleotides targeted to RhoA.

Thus, Cowsert discloses all limitations of and anticipates claims 120, 127-129 and 131.

Claims 1-13, 16-27, 29, 44-51, 53 and 87-119 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US 6,506,559, cited on IDS).

The claims are directed to methods of inhibiting expression of target genes in cells that may be in an organism using double stranded RNA. The RNA hybridizes with or is identical to all or a portion of the target gene; the target gene is endogenous, cellular, foreign, viral or from a pathogen. The RNA may be formed from a single strand or separate complementary strands.

Fire et al. disclose a method of attenuating expression of a target gene *in vitro* in a cell using double stranded RNA. The disclosure and claims of Fire et al. are drawn to plant and animal cells, including mammalian and primate cells (see column 8, lines 35-51 and claims 6 and 7), the genes targeted can be endogenous or can be from a pathogen (see column 6, lines 45-49 and claims 3 and 4). The dsRNA can be formed from 1 or 2 strands (see column 4, lines 41-46). The dsRNA can be introduced into cells by a vector or by using lipid carriers or calcium precipitating agents (see column 9, lines 49-59). Fire et al. do not disclose a length limitation of the size of the dsRNA or a necessary degree of gene attenuation, so RNA sequences of 20 nucleotides in length and 10-fold attenuation are all encompassed by the claims of Fire et al.

Thus, Fire et al. disclose all limitations of and anticipate claims 1-13, 16-27, 29, 44-51, 53 and 87-119.

Claims 1, 7-10, 16-18, 22, 23, 76, 80-82, 87-89, 92 and 107 are rejected under 35 U.S.C. 102(e) as being anticipated by Graham (US 6,573,099).

The claimed invention is directed to methods of inhibiting expression of target genes in cells that may be in an organism using double stranded RNA. The RNA may be a single self-complementary strand or two separate strands and may be produce inside or outside of the cell by transcription from an expression construct.

Graham discloses genetic constructs containing multiple copies of genes and claims a method of reducing expression of a target gene in an animal cell using an expression construct containing two or more copies of a structural gene (see in particular claim 10). The animal cells claimed by Graham include mammals such as

human. The plasmids of Graham are double stranded and hence contain a region that is identical to the endogenous gene.

Thus, Graham discloses all limitations of and anticipates claims 1, 7-10, 16-18, 22, 23, 76, 80-82, 87-89, 92 and 107.

Claims 120-125 and 127 are rejected under 35 U.S.C. 102(e) as being anticipated by Brown et al. (US 2004/0029275).

The claimed invention is directed to methods of inhibiting gene expression in a cell, including mammalian cells, using a combination of two or more RNA function inhibitors specific for a target gene. The RNA function inhibitors may be siRNAs that may be transcribed from an expression cassette.

Brown et al. disclose a method of gene silencing in a cell using "cocktails" containing numerous double stranded RNAs. At paragraph 21 Brown et al. disclose that the double stranded RNA is 21-25 bases in length. At paragraph 35 Brown et al. disclose that the cell may be a mammalian cell. Brown et al. disclose that these cocktails may be produced from expression constructs. Because an siRNA contains a sequence that is antisense to the target gene, such constructs would encode an antisense sequence.

Thus, Brown et al. disclose all limitations of and anticipate claims 120-125 and 127.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 120-129 and 131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cowsert as applied to claims 120, 127-129 and 131 above, and further in view of Brown et al.

Claims 120-125, 127-129 and 131 are described in the 102 rejections over Cowsert and Brown et al. Claim 126 is directed to a method of inhibiting gene expression using a combination of an antisense polynucleotide and an siRNA.

Cowsert teaches antisense oligonucleotides directed to RhoA and additionally teaches that RhoA expression can be inhibited by administration of multiple antisense oligonucleotides targeted to RhoA. Cowsert does not teach inhibition of gene expression using siRNA or the combination of siRNA and antisense polynucleotides.

Brown et al. teach a method of gene silencing in a cell using "cocktails" containing numerous siRNAs. In an exemplified embodiment, Brown et al. teach that siRNAs inhibit expression of Rho.

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Brown et al. and Cowsert to inhibit gene expression in a cell using a combination of an antisense polynucleotide and an siRNA. A person of ordinary skill in the art would have been motivated to do so because Brown

et al. teach that gene expression can be inhibited with siRNAs and Cowsert teaches that antisense polynucleotides can be used to inhibit gene expression. Further, section 2144.06 of the MPEP states the following:

> "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

A person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Brown et al. and Cowsert because each of their teachings are directed to the same purpose and each of them demonstrate that their individual teachings function for their intended purpose.

Thus, claims 120-129 and 131 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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TV
January 3, 2006

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PATENT EXAMINER